Best of Intent, Worst of Both Worlds: Why Sequentially Combining Epidemiological Methods Does Not Improve Signal Detection in Vaccine Surveillance

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INTRO

- There is a clinical intuition that combining sensitive and specific methods will improve vaccine safety signal detection.
- Little is known on the comparative performance of methods with real-world data.

METHODS

1. We evaluated six vaccine exposures: H1N1pdm, seasonal flu (Fluvirin), seasonal flu (Fluzone), seasonal flu (All), zoster (Shingrix), HPV (Gardasil 9) across four databases (CCAE, IBM MDCR, IBM MDCD, Optum EHR).
2. All data partners used the Observational Medical Outcomes Partnership (OMOP) common data model (CDM).
3. We generated a set of negative control and imputed positive control outcomes.
4. We defined a time-at-risk of 1-28 days after vaccination.
5. We used R programming to compute and compare the one-sided *p* values and type I and II errors (with and without empirical calibration) of a highly sensitive method (historical comparator), a highly specific method (self-controlled case series), and a method that sequentially combines the two.

RESULTS

- Using a highly sensitive method followed by a highly specific method did not compensate for the individual flaws of each method alone.

Applying a sensitive method followed by a specific method **does not improve signal detection** for adverse events under vaccine surveillance.

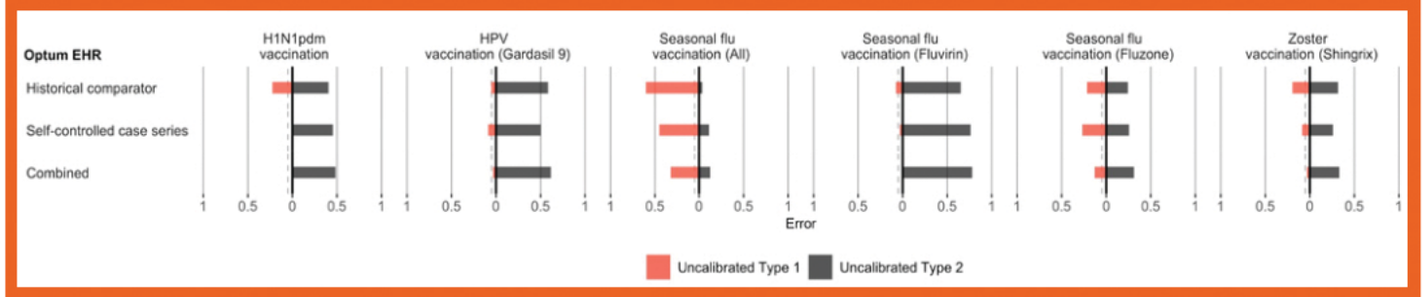

Figure 1. Type I and II errors (before empirical calibration) for all outcomes in Optum EHR. Historical comparator tends to be more sensitive, and SCCS tends to be more specific. Sequentially combining them increases specificity and decreases sensitivity.

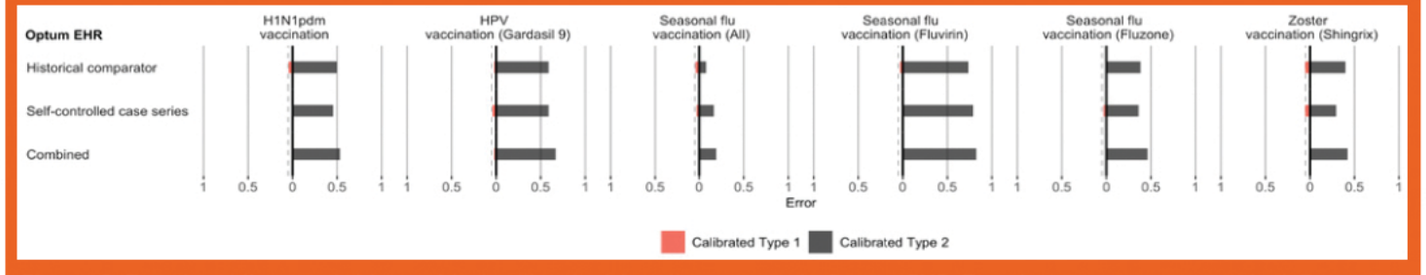

Figure 2. Type I and II errors (with empirical calibration) for all outcomes in Optum EHR. Type I errors return to nominal. Even with calibration, combining historical comparator and SCCS using the serial approach does not improve both sensitivity and specificity.

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ADDITIONAL RESULTS

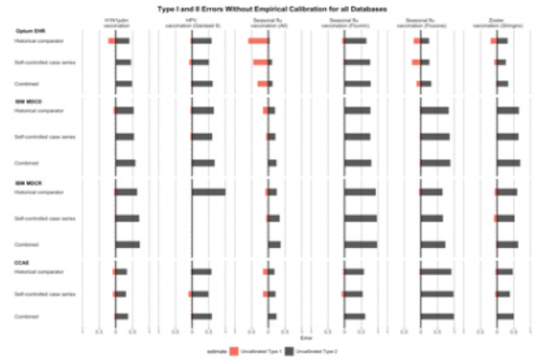

Figure 3. Type I and II errors without empirical calibration across databases. Historical comparator is not always more sensitive than SCCS, and SCCS is not always more specific than historical comparator.

Figure 4. Type I and II errors for all outcomes with empirical calibration across databases. Type I error returns to nominal.

DISCUSSION

- The use of real-world data mapped to the CDM allows for replicability and transparency.
- One limitation was the lack of COVID-19 vaccine exposures.

CONCLUSION

- Our findings oppose clinical advice to use a serial method in signal detection.

AUTHORS

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